Oxidative response gene polymorphisms and risk of adult brain tumors

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Oxidative stress is believed to play a key role in tumor formation. Although this mechanism could be especially pertinent for brain tumors given the high oxygen consumption of the brain, very little has been published regarding brain tumor risk with respect to genes mediating oxidative stress. Using data from non-Hispanic whites in a hospital-based case-control study conducted by the National Cancer Institute between 1994 and 1998, we evaluated risk of glioma (*n* = 362), meningioma (*n* = 134), and acoustic neuroma (*n* = 69) compared to noncancer controls (*n* = 494) with respect to nine single nucleotide polymorphisms from seven genes involved in oxidative stress response (*CAT*, *GPX1*, *NOS3*, *PON1*, *SOD1*, *SOD2*, and *SOD3*). We observed increased risk of glioma (odds ratio [OR]$_{CT/CC}$ = 1.3; 95% confidence interval [95% CI], 1.0–1.7) and meningioma (OR$_{CT/CC}$ = 1.7; 95% CI, 1.1–2.7) with the C variant of *SOD3* rs699473. There was also indication of increased acoustic neuroma risk with the *SOD2* rs4880 *Ala* variant (OR$_{CT/CC}$ = 2.0; 95% CI, 1.0–4.2) and decreased acoustic neuroma risk with the *CAT* rs1001179 T allele variant (OR$_{CT/TT}$ = 0.6; 95% CI, 0.3–1.0). These relationships persisted when major groups of disease controls were excluded from the analysis. Our results suggest that common variants in the *SOD2*, *SOD3*, and *CAT* genes may influence brain tumor risk. *Neuro-Oncology 10, 709–715, 2008 (Posted to Neuro-Oncology [serial online], Doc. 08-00008, August 4, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-037)*

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Oxygen-free radicals contain unpaired electrons in their outer orbit and are thus highly reactive with other chemical species.[1] Although oxygen is crucial for respiration and the energy processes that enable life, healthy aerobes must maintain a balance between the formation of reactive oxygen species and antioxidant defenses. Evidence from in vitro, animal, and human studies indicates that oxygen free radicals play a key role in several pathological conditions, including cardiovascular disease, neurological disorders, aging, and cancer.[1–3] The oxidative stress mechanism is of particular interest in brain tumors given the high rate of oxygen metabolism in the brain compared to other

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organs.[4] Additionally, ionizing radiation, which is the only known environmental risk factor for brain tumors, is believed to cause much of its DNA damage through the formation of reactive oxygen species.[5] Given the increasing evidence that immune factors are important in brain tumor etiology,[6] it is also relevant that reactive oxygen species defend against infection in the innate immune system and coordinate the inflammatory response.[4]

Several enzymes function to prevent or mitigate damage caused by reactive oxygen species, including superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), nitric oxide synthase (NOS), and paraoxonase (PON). In this study, we evaluated the risk of glioma, meningioma, and acoustic neuroma associated with single nucleotide polymorphisms (SNPs) in genes involved in oxidative stress response.

Materials and Methods

Study Setting and Population

A detailed description of study methods can be found elsewhere.[7] Briefly, eligible patients were 18 or more years of age with a first intracranial glioma, meningioma (International Classification of Diseases–Oncology, version 2 [ICD-O-2] codes 9530–9538), or acoustic neuroma (ICD-O-2 codes 9560) diagnosed during 1994–1998 at one of three hospitals specializing in brain tumor treatment (in Boston, Phoenix, and Pittsburgh) within the 8 weeks preceding hospitalization. Ninety-two percent of eligible brain tumor patients agreed to participate, and 489 patients with glioma, 197 with meningioma, and 96 with acoustic neuroma were enrolled, with all but 4% of the acoustic neuromas being confirmed by microscopy.

Controls were admitted to the same hospitals for injuries (25%), circulatory system disorders (22%), musculoskeletal disorders (22%), digestive disorders (12%), or a variety of other nonneoplastic conditions and were frequency-matched in a 1:1 ratio to all brain tumor patients based on age group (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–99 years), race/ethnicity (non-Hispanic white, Hispanic, African-American, other), sex, hospital, and residential proximity to the hospital. A total of 799 control patients (86% of all contacted) were enrolled. The study protocol was approved by the institutional review board of each participating institution, and written informed consent was obtained from each patient or proxy. This analysis was restricted to non-Hispanic whites (89% of all study participants) who provided blood samples. For non-Hispanic whites who had consented to provide blood samples, samples were genotyped for 362 patients with glioma (74% of all non-Hispanic whites), 134 patients with meningioma (68%), 69 patients with acoustic neuroma (72%), and 494 controls (62%). The main obstacle to obtaining blood samples was subject refusal, with nonparticipation in the blood draw being higher for controls (24%) than for cases (14%).

Processing of Blood Samples and Genotyping

Polymorphisms in genes in the oxidative stress pathway were selected based on minor allele frequency >0.05 according to the SNP500Cancer database,[8] putative functional importance, and/or evidence of an association with cancer risk (Table 1). Results are reported for all selected SNPs. DNA was extracted using a phenol-chloroform method, and genotyping was conducted using a medium-throughput TaqMan assay (http://snp500cancer.nci.nih.gov).[8] Each plate of 368 specimens included homozygous wild-type, heterozygous and homozygous variant positive controls, and one DNA negative control. Quality control specimens included 15–34 samples from three nonstudy participants and duplicates from 89 study subjects that were interspersed among all genotyping assays in a masked fashion. Percent agreement among the three nonstudy replicates ranged from 97.9% to 100% for all SNPs. Concordance for duplicates was 99.3% for *SOD2* rs4880 and *GPX1* rs1800668, and 100% for the remaining seven SNPs. The genotyping success rate for the nine SNPs ranged from 95.6% to 99.2%, and Hardy-Weinberg equilibrium in controls showed no significant deviation except for the *PON1* rs662 ($p = 0.04$) and *CAT* rs769214 ($p = 0.02$) polymorphisms.

Statistical Analyses

Statistically significant departure from Hardy-Weinberg equilibrium for controls was assessed using the chi-square test. For each polymorphism, unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for each major tumor type and for glioblastoma cases, adjusted for the study matching factors of age, sex, hospital, and residential proximity to hospital. Because controls were frequency matched to all tumor types, all controls were used in the models for each tumor type. Models were run under the assumption of codominant (AA vs. Aa vs. aa), dominant (AA vs. Aa or aa), and recessive (AA or Aa vs. aa) inheritance. A score test of linear trend was conducted for each SNP using a three-level ordinal variable. In order to evaluate possible bias introduced by using disease controls, regression models were repeated for each SNP, excluding one set of disease controls at a time. Adjusted *p*-values taking into account multiple comparisons within each tumor type were calculated using the false discovery rate.[9]

Results

Genotyped subjects, 1,169 (82%) of the 1,411 non-Hispanic white participants, were similar to all study subjects except for the lower proportion of those 70–90 years of age and those with less education. Compared to controls, a higher proportion of glioma subjects were male, whereas subjects with meningioma and acoustic neuroma showed a female predominance and were, on average, older than controls (Table 2).

The *SOD3* IVS1+186C>T polymorphism (rs699473) was associated with significantly increased risk of men-

Table 1. Oxidative stress genes and single nucleotide polymorphisms evaluated in the National Cancer Institute Adult Brain Tumor Study

Gene Symbol	Gene Name	Location	SNP500 Nucleotide and/or Amino Acid Change	Downstream Binding Site (DBS) Sequence	Function
CAT	Catalase	11p13	–329T>C –843A>G	rs1001179 rs769214	Enzyme converts hydrogen peroxide to water and oxygen; high-activity –329C allele associated with lower risk of breast cancer[25]
GPX1	Glutathione peroxidase 1	3p21.3	Ex1–226C>T (P200L) Ex1+35C>T	rs1050450 rs1800668	Enzyme detoxifies hydrogen peroxide to form water and oxygen; –226T allele (*Leu* variant) associated with increased risk of non-Hodgkin lymphoma,[23] lung cancer,[29] bladder cancer,[30] and possibly breast cancer[31,32]
NOS3	Nitric oxide synthase 3	7q36	Ex8–63T>G (D298E)	rs1799983	Enzyme forms nitric oxide during conversion of L-arginine to L-citrulline
PON1	Paraoxonase 1	7q21.3	Ex6+78A>G (Q192R)	rs662	Enzyme binds to high-density lipoprotein and contributes to detoxification of organophosphorus compounds and other lipid-soluble radicals; increased risk of prostate cancer,[33] breast cancer,[34] and childhood brain cancer[28] with different single nucleotide polymorphisms in the *PON1* gene
SOD1	Superoxide dismutase 1, soluble	21q22.11	IVS3–251A>G	rs2070424	Enzyme catalyzes dismutation of superoxide radical to hydrogen peroxide
SOD2	Superoxide dismutase 2, mitochondrial	6q25.3	Ex2+24T>C (V16A)	rs4880	Enzyme catalyzes dismutation of superoxide radical to hydrogen peroxide; single nucleotide polymorphisms alters manganese superoxide dismutase expression; *Ala* variant associated with increased risk of breast cancer,[16] prostate cancer,[17,18] ovarian cancer,[19] bladder cancer,[20] non-Hodgkin lymphoma,[13] mesothelioma,[14] and hepatic carcinoma[15]
SOD3	Superoxide dismutase 3, extracellular	4p16.3–q21	IVS1+186C>T	rs699473	Enzyme catalyzes dismutation of superoxide radical to hydrogen peroxide

Table 2. Demographic characteristics in non-Hispanic white participants with genotyping results: National Cancer Institute Adult Brain Tumor Study, 1994–1998

Characteristic	Glioma (*n* = 362)	Meningioma (*n* = 134)	Acoustic Neuroma (*n* = 69)	Controls (*n* = 494)
Sex, *n* (%)				
Male	198 (54.7)	30 (22.4)	25 (36.2)	227 (46.0)
Female	164 (45.3)	104 (77.6)	44 (63.8)	267 (54.1)
Age at interview, *n* (%)				
18–29 years	41 (11.3)	1 (0.8)	3 (4.4)	55 (11.1)
30–49 years	137 (37.9)	53 (39.6)	27 (39.1)	209 (42.3)
50–69 years	121 (33.4)	57 (42.5)	31 (44.9)	171 (34.6)
70–90 years	63 (17.4)	23 (17.6)	8 (11.6)	59 (11.9)
Age at interview, mean, (median) years	51.2 (50)	54.8 (54)	51.7 (53)	49.2 (48)

ingioma (OR_{CT} = 1.7; 95% CI, 1.1–2.7; OR_{CC} = 2.1; 95% CI, 1.0–4.1; *p*-trend = 0.01) and possible increased risk of glioma (OR_{CT} = 1.3; 95% CI, 0.95–1.7; OR_{CC} = 1.2; 95% CI, 0.7–2.0; *p*-trend = 0.2) (Table 3). Elevated glioma risk with the *SOD3* variant was less pronounced when analyses were restricted to glioblastoma only (*n* = 166; OR_{CT} = 1.1; 95% CI, 0.7–1.6; OR_{CC} = 1.3; 95% CI, 0.7–2.4; $OR_{CT/CC}$ = 1.3; 95% CI, 0.7–2.3; *p*-trend = 0.5). A suggestion of increased risk of acoustic neuroma was observed with the *SOD2* rs4880 variant (OR_{CT} = 2.1; 95% CI, 1.0–4.5; OR_{CC} = 1.9; 95% CI, 0.8–4.6; *p*-trend = 0.2), and there was some indication of decreased acoustic neuroma risk with the *CAT* rs1001179 variant (OR_{CT} = 0.5; 95% CI, 0.3–1.0; OR_{TT} = 0.7; 95% CI, 0.2–2.7; *p*-trend = 0.1). We observed no significant association between genotype and risk of glioma, glioblastoma, meningioma, or acoustic neuroma for the remaining polymorphisms. Results remained very similar in models adjusting for all other SNPs and when major groups of disease controls were excluded from the analysis, one at a time. After controlling for multiple comparisons using the false discovery rate, only the association between meningioma and *SOD3* rs699473 remained of borderline significance (*p* = 0.09).

Table 3. Odds ratios for oxidative stress gene single nucleotide polymorphisms in non-Hispanic whites in the National Cancer Institute Adult Brain Tumor Study, 1994–1998 (adjusted for age, sex, study site, distance of residence from hospital)

				Glioma		Meningioma		Acoustic Neuroma	
Gene Polymorphism	Chromosomal Location	Genotype	Controls (*n*)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)
CAT	11p13	CC	251	195	1.0 (ref)	73	1.0 (ref)	43	1.0 (ref)
rs1001179		CT	164	124	1.0 (0.7, 1.4)	39	0.8 (0.5, 1.2)	17	0.5 (0.3, 1.0)
		TT	23	11	0.6 (0.3, 1.3)	8	1.2 (0.5, 3.0)	3	0.7 (0.2, 2.7)
					p-trend = 0.5		*p*-trend = 0.6		*p*-trend = 0.1
		CT or TT	187	135	1.0 (0.7, 1.3)	47	0.8 (0.5, 1.3)	20	0.6 (0.3, 1.0)*
		CC or CT	415	319	1.0 (ref)	112	1.0 (ref)	60	1.0 (ref)
		TT	23	11	0.6 (0.3, 1.3)	8	1.4 (0.6, 3.3)	3	0.9 (0.3, 3.4)
CAT	11p13	AA	208	158	1.0 (ref)	52	1.0 (ref)	28	1.0 (ref)
rs769214 [a]		AG	219	156	0.9 (0.7, 1.2)	61	1.1 (0.7, 1.8)	28	0.9 (0.5, 1.7)
		GG	33	24	1.0 (0.5, 1.7)	7	0.9 (0.3, 2.1)	6	1.2 (0.4, 3.1)
					p-trend = 0.7		*p*-trend = 0.9		*p*-trend = 1.0
		AG or GG	252	180	0.9 (0.7, 1.2)	68	1.1 (0.7, 1.7)	34	1.0 (0.5, 1.7)
		AA or AG	427	314	1.0 (ref)	113	1.0 (ref)	56	1.0 (ref)
		GG	33	24	1.0 (0.6, 1.8)	7	0.8 (0.3, 1.9)	6	1.2 (0.5, 3.1)
GPX1	11q13	CC	236	165	1.0 (ref)	57	1.0 (ref)	28	1.0 (ref)
rs1050450		CT	178	140	1.1 (0.8, 1.5)	56	1.2 (0.8, 1.9)	30	1.4 (0.8, 2.4)
		TT	46	35	1.0 (0.6, 1.7)	10	0.9 (0.4, 2.0)	7	1.5 (0.6, 3.8)
					p-trend = 0.7		*p*-trend = 0.7		*p*-trend = 0.3
		CT or TT	224	175	1.1 (0.8, 1.4)	66	1.2 (0.8, 1.8)	37	1.4 (0.8, 2.4)
		CC or CT	414	305	1.0 (ref)	113	1.0 (ref)	58	1.0 (ref)
		TT	46	35	1.0 (0.6, 1.6)	10	0.8 (0.4, 1.8)	7	1.3 (0.5, 3.1)
GPX1	11q13	CC	218	156	1.0 (ref)	56	1.0 (ref)	27	1.0 (ref)
rs1800668		CT	171	132	1.1 (0.8, 1.5)	52	1.1 (0.7, 1.7)	29	1.3 (0.7, 2.3)
		TT	50	40	1.1 (0.7, 1.7)	12	0.9 (0.4, 1.9)	7	1.3 (0.5, 3.3)
					p-trend = 0.7		*p*-trend = 1.0		*p*-trend = 0.4
		CT or TT	221	172	1.1 (0.8, 1.4)	64	1.1 (0.7, 1.6)	36	1.3 (0.7, 2.2)
		CC or CT	389	288	1.0 (ref)	108	1.0 (ref)	56	1.0 (ref)
		TT	50	40	1.0 (0.7, 1.6)	12	0.9 (0.4, 1.8)	7	1.2 (0.5, 2.8)
NOS3	7q36	GG	204	157	1.0 (ref)	52	1.0 (ref)	33	1.0 (ref)
rs1799983		GT	202	148	1.0 (0.7, 1.3)	57	1.0 (0.6, 1.6)	25	0.7 (0.4, 1.4)
		TT	61	35	0.7 (0.5, 1.2)	14	0.8 (0.4, 1.6)	5	0.5 (0.2, 1.5)
					p-trend = 0.3		*p*-trend = 0.7		*p*-trend = 0.2
		GT or TT	263	183	0.9 (0.7, 1.2)	71	1.0 (0.6, 1.5)	30	0.7 (0.4, 1.2)
		GG or GT	406	305	1.0 (ref)	109	1.0 (ref)	58	1.0 (ref)
		TT	61	35	0.8 (0.5, 1.2)	14	0.8 (0.4, 1.6)	5	0.6 (0.2, 1.6)
PON1	7q21	AA	244	163	1.0 (ref)	74	1.0 (ref)	29	1.0 (ref)
rs662 [a]		AG	165	143	1.3 (0.9, 1.7)	37	0.7 (0.4, 1.1)	27	1.5 (0.8, 2.7)
		GG	44	26	0.9 (0.5, 1.5)	9	0.7 (0.3, 1.6)	4	0.8 (0.2, 2.4)
					p-trend = 0.6		*p*-trend = 0.2		*p*-trend = 0.7
		AG or GG	209	169	1.2 (0.9, 1.6)	46	0.7 (0.5, 1.1)	31	1.3 (0.7, 2.3)
		AA or AG	409	306	1.0 (ref)	111	1.0 (ref)	56	1.0 (ref)
		GG	44	26	0.8 (0.5, 1.3)	9	0.8 (0.4, 1.8)	4	0.6 (0.2, 1.9)
SOD1	21q22	AA	414	303	1.0 (ref)	112	1.0 (ref)	60	1.0 (ref)
rs2070424		AG	55	37	0.9 (0.6, 1.4)	12	0.7 (0.4, 1.5)	4	0.4 (0.1, 1.3)
		GG	0	2	—	0	—	1	—
					p-trend = 0.9		*p*-trend = 0.4		*p*-trend = 0.5
		AG or GG	55	39	0.9 (0.6, 1.4)	12	0.7 (0.4, 1.5)	5	0.6 (0.2, 1.5)
		AA or AG	469	340	1.0 (ref)	124	1.0 (ref)	64	1.0 (ref)
		GG	0	2	—	0	—	1	—

Table 3. (*continued*)

Gene Polymorphism	Chromosomal Location	Genotype	Controls (*n*)	Glioma *n*	Glioma OR (95% CI)	Meningioma *n*	Meningioma OR (95% CI)	Acoustic Neuroma *n*	Acoustic Neuroma OR (95% CI)
SOD2	6q25	TT	122	80	1.0 (ref)	39	1.0 (ref)	10	1.0 (ref)
rs4880		CT	220	167	1.1 (0.8, 1.6)	61	0.9 (0.6, 1.5)	34	2.1 (1.0, 4.5)
		CC	109	86	1.1 (0.8, 1.7)	21	0.6 (0.3, 1.1)	16	1.9 (0.8, 4.6)
					p-trend = 0.5		*p*-trend = 0.1		*p*-trend = 0.2
		CT or CC	329	253	1.1 (0.8, 1.6)	82	0.8 (0.5, 1.3)	50	2.0 (1.0, 4.2)*
		TT or CT	342	247	1.0 (ref)	100	1.0 (ref)	44	1.0 (ref)
		CC	109	86	1.1 (0.8, 1.5)	21	0.6 (0.4, 1.1)	16	1.1 (0.6, 2.2)
SOD3	4p15	TT	210	134	1.0 (ref)	41	1.0 (ref)	32	1.0 (ref)
rs699473		CT	204	166	1.3 (0.95, 1.7)	65	1.7 (1.1, 2.7)*	31	1.0 (0.5, 1.7)
		CC	48	38	1.2 (0.7, 2.0)	17	2.1 (1.0, 4.1)*	2	—
					p-trend = 0.2		*p*-trend = 0.01*		*p*-trend = 0.1
		CT or CC	252	204	1.3 (1.0, 1.7)*	82	1.7 (1.1, 2.7)*	33	0.8 (0.5, 1.4)
		TT or CT	414	300	1.0 (ref)	106	1.0 (ref)	63	1.0 (ref)
		CC	48	38	1.1 (0.7, 1.7)	17	1.6 (0.8, 3.0)	2	—

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; ref, reference group.

[a]Controls not in Hardy-Weinberg equilibrium ($p = 0.04$ for *PON1* rs662, $p = 0.02$ for *CAT* rs769214).

*Significant (or borderline significant) at the $p < 0.05$ level.

Discussion

SOD enzymes, which catalyze the spontaneous dismutation of the superoxide radical to hydrogen peroxide, are present in all parts of the nervous system, including the mitochondrial intermembrane space (SOD1; copper/zinc SOD), the mitochondrial matrix (SOD2; manganese SOD), and the plasma, lymph, and synovial fluid (SOD3; extracellular SOD).[4,10] Red-blood-cell activity levels of SOD have been shown to be decreased for most types of intracranial neoplasm.[11] The functionality of the *SOD3* IVS1+186C>T polymorphism, for which we observed increased risk of meningioma and glioma, has not been characterized. The *SOD2 Ala* variant, on the other hand, occurs at a mitochondrial targeting sequence and allows more efficient SOD2 enzyme uptake into the mitochondrial matrix, generating more active SOD2 compared with the *Val* variant.[12] We observed increased risk of acoustic neuroma with the *SOD2* (V16A) *Ala* (C allele) variant, consistent with the known functionality of the polymorphism, as well as previous studies that have observed increased risk of non-Hodgkin lymphoma,[13] mesothelioma,[14] hepatic carcinoma,[15] and breast,[16] prostate,[17,18] ovarian,[19] and bladder cancers[20] with the *Ala* variant. Other cancer studies, however, have observed no association (lung, breast cancer)[21,22] or significantly decreased risk (marginal zone lymphoma)[23] with the *Ala* allele. In a prospective study of prostate cancer, the *SOD2* V16A polymorphism did not have an overall effect, but strongly modified the relationship between prediagnostic serum antioxidant level and risk of prostate cancer.[24] We observed no associations with the *SOD1* variant and brain tumors, consistent with no association noted with *SOD1* variants and prostate cancer.[17]

The enzyme CAT catalyzes the degradation of hydrogen peroxide into water and molecular oxygen and is found mainly in the peroxisomes but may also appear in plasma. Individuals with the common CC genotype of the *CAT* rs1001179 variant have been shown to have significantly higher CAT activity compared with individuals with the T variant, and the high-activity CC CAT genotype has been associated with a significantly reduced risk of breast cancer, especially with high consumption of fruits and vegetables.[25,26] We saw some indication of reduced risk of acoustic neuroma with the TT (low-activity) allele, but the lack of statistically significant trend and the unexpected direction of risk suggest that this may be a chance finding.

The *PON1* gene codes for the PON enzyme, which binds to high-density lipoprotein and contributes to the detoxification of organophosphates and lipid-soluble radicals from lipid peroxidation. Serum activity levels of PON1 have been shown to be lower in glioma and meningioma patients than in controls.[27] A previous study of childhood brain tumors observed a nonstatistically significant increase in risk with the *PON1* –108T allele, which became stronger and statistically significant when restricted to children whose mothers reported chemical treatment of the home for pests during pregnancy or childhood. The same study observed no association with the *PON1* Q192R polymorphism.[28] While we did not assess the –108T polymorphism and hence cannot compare results for that polymorphism, we detected no association with the Q192R polymorphism.

This study had adequate statistical power to detect

moderate to strong main effects (OR $\geq$ 1.5) of common genetic polymorphisms for glioma and meningioma. After controlling for multiple comparisons using the false discovery rate, however, only the association between meningioma and SOD3 rs699473 remained of borderline significance. Strengths include standardized genotyping, high reproducibility of the genotyping results in the quality control samples, and controls in Hardy-Weinberg equilibrium for all but two polymorphisms. Given that deviation from Hardy-Weinberg equilibrium was not extreme ($p < 0.01$) for either of these polymorphisms and that we observed no significant associations for the two SNPs in question, this is unlikely to affect our results. Rapid ascertainment of brain tumor cases and blood collection close to the date of diagnosis reduced the possibility that survival bias affected our results. Results of the analyses were very similar after excluding major groups of disease controls, one at a time.

Nevertheless, we underscore the need for replication of our findings given the false-positive reports generated in genetic association studies or the possibility that the notable SNPs are actually in linkage disequilibrium with other causally relevant polymorphisms. While nonparticipation in the blood draw was higher among controls than cases, we believe that this is unlikely to be related to genotype, and thus unlikely to bias our results.

Our findings suggest that *SOD3*, *SOD2*, and *CAT* may be promising candidates for brain tumor susceptibility genes and provide support for a role of the innate immune system in brain tumor etiology. Future research in this area should include more detailed coverage of polymorphisms within the genes implicated in this study, as well as other genes involved in the mediation of oxidative stress response.

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